Epidemiology of measles in infants younger than 6 months: analysis of surveillance data 2011-2016

An analysis of the epidemiology of measles in infants younger than 6 months was conducted by the U.S. CDC and WHO using case-based measles surveillance data from 2011 to 2016. The specific research questions for this analysis were:

1. What is the burden of disease due to measles among infants less than 6 months old?
2. What epidemiological circumstances and country situations are associated with a significant proportion of children <6 months old affected?

Methods

The analyses were conducted using case-based measles surveillance data that were available at WHO-HQ for years of onset 2011-2016, except for the South-East Asia Region (SEAR) for which surveillance data were available only for 2014-2016. Confirmed measles cases were defined as cases that were either laboratory confirmed or epidemiologically linked to a confirmed case. The percentage of cases <6 months was calculated using the number of cases with known age as the denominator (i.e., cases that were missing age were excluded from the denominator). Age-specific annual incidence per 1 million population was calculated as the 6-year average (2011-2016), except in SEAR countries for which the 3-year average annual incidence was calculated. Incidence calculations used UNDP population estimates.[1]

Surveillance data from several countries were excluded from analysis due to small numbers of confirmed cases (n=32 countries excluded because they had <30 confirmed cases during 2011-2016) or case ages were only reported in full years (n=36 countries excluded; 30 EUR countries excluded, all SEAR countries except India excluded) (Figure 1). Further, although surveillance data from India were included in the epidemiologic analysis, India surveillance data were excluded from the regression analysis because case-based surveillance was not fully implemented in India during the time period of study, so it cannot be ensured that the data is representative of all measles cases in India.

[1] UNDP 2015 revision population data.

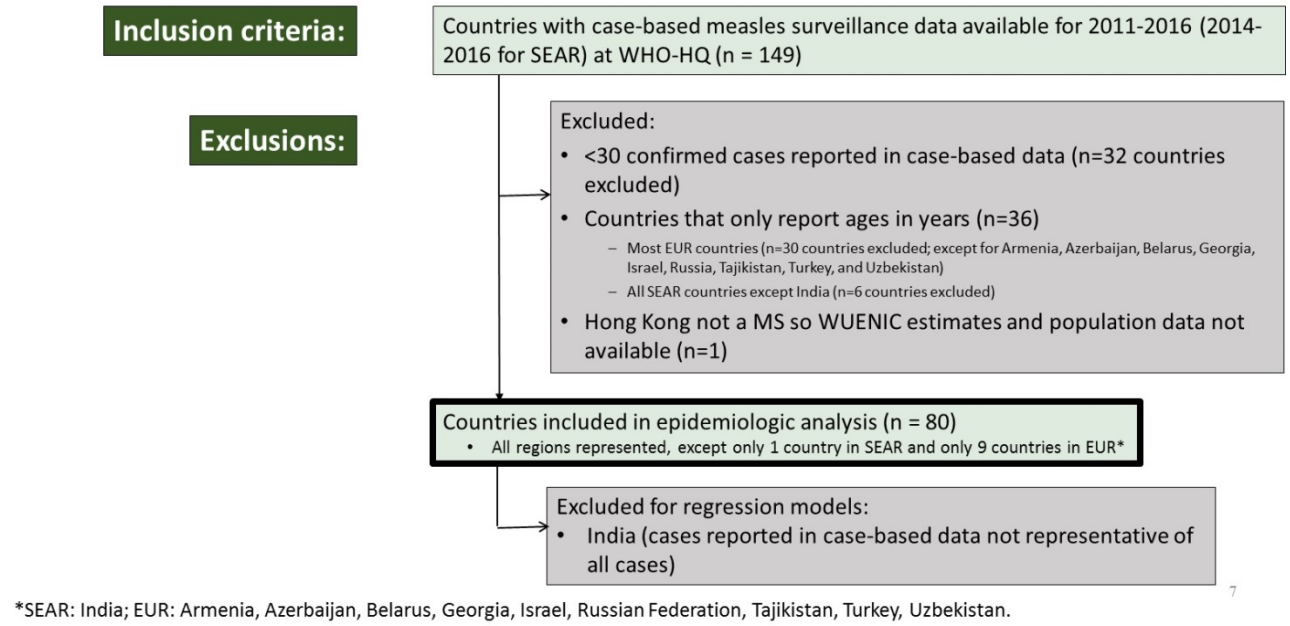


Figure 1. Inclusion and exclusion criteria for analysis of epidemiology of measles in infants younger than 6 months.

Part 1 of the study was an epidemiologic analysis to assess the scale of measles epidemiology among infants <6 months during 2011-2016. This included a descriptive analysis of infant cases and the country contexts. We calculated absolute numbers of confirmed measles cases among this age group, <6-month cases as a proportion of all measles cases, and age-specific annual measles incidence.

Part 2 of the study was a comparative analysis using bivariate and multivariate regression analyses. The purpose was to evaluate associations between country/programmatic characteristics and measles cases among infants <6 months. Country/programmatic characteristics were used as independent variables, and included the following variables:

- WHO region
- World Bank income classification (2011)
- MCV1 and MCV2 coverage (2007-2011 5-year average)
- MCV1 and MCV2 year of introduction
- MCV1 and MCV2 age of administration (as reported in 2016 JRF submission)
- SIAs in recent years
- Population density (persons per km^2, based on UNDP estimates for 2011)
- Birth rate (births per 1,000 population, based on UNDP estimates for 2010-2015)

There were three measures of infant measles that we were interested in. These measures were: 1) incidence per million among infants <6 months (a continuous variable), 2) proportion of cases among infants <6 months (a continuous variable), and 3) a pre-determined cut-off for a “high” proportion of cases among infants <6 months ($\geq$5% versus <5%). We used poisson regression, beta regression, and logistic regression models, respectively, to estimate associations of the country/programmatic characteristics listed above with these three measures.

Results

Epidemiology of measles among infants <6 months

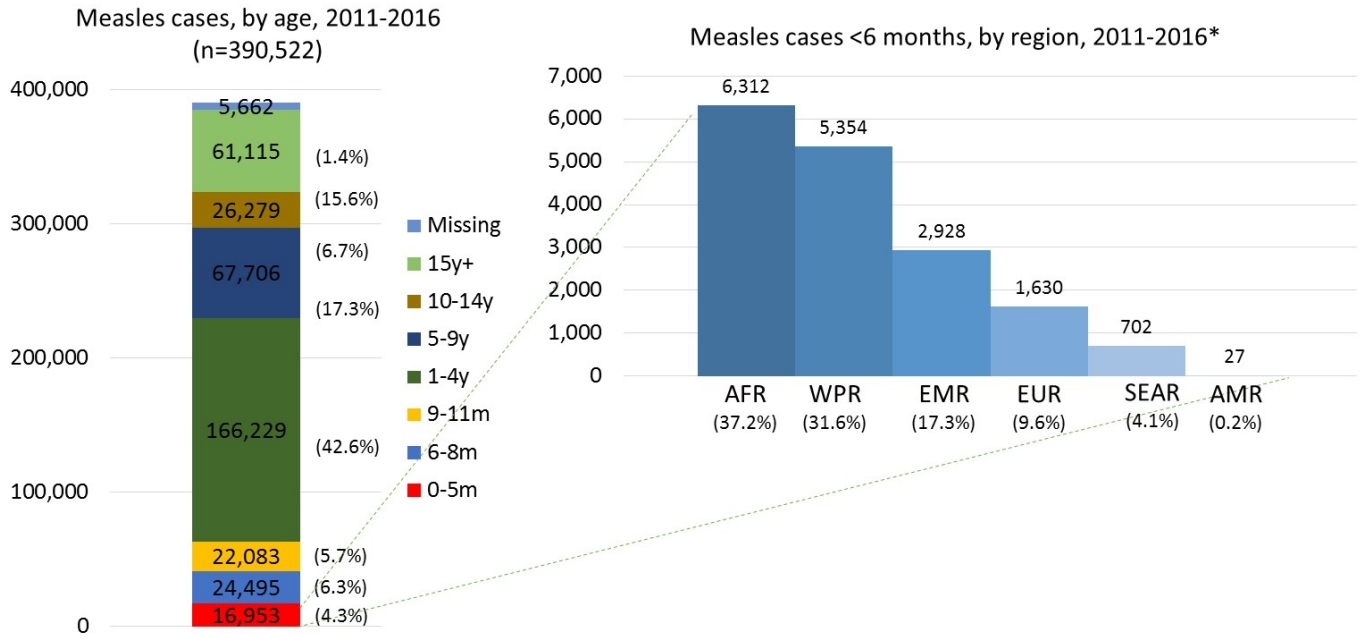


Figure 2. Ages of confirmed measles cases, and cases age <6 months by region, 2011-2016.

There were a total of 390,522 confirmed* measles cases of all ages during 2011-2016 in the countries included in analysis. Of all cases, 16,953 (4.3%) were among infants <6 months (Figure 2). The largest numbers of measles cases <6 months were in countries in the African Region (AFR; 6,312 cases, 37.2%) and the Western Pacific Region (WPR; 5,354, 31.6%). This figure under-represents cases in the South-East Asian Region (SEAR) and the European Region (EUR) because most countries in those regions were excluded due to case ages only reported in full years.

Compared to other age groups, <6-month infants are overrepresented among measles cases. Although infants <6 months comprise 1.2% of the population, infants <6 months comprised 4.3% of all cases in these countries.

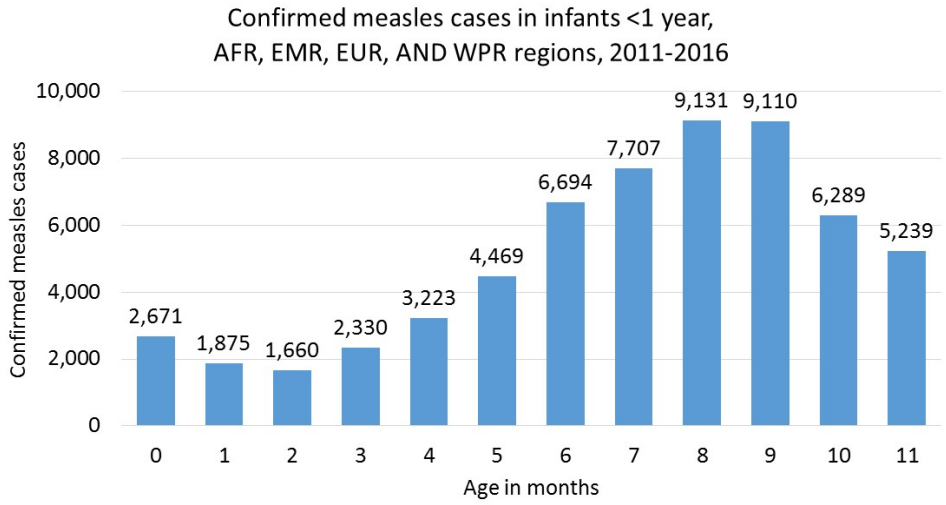


Figure 3. Confirmed measles incidence per 1 million population by age in months, among infants <12 months of age, 2011-2016.

In general, the number of measles cases at each age in months (e.g., <1-month-olds, 1-month-olds, 2-month-olds, 3-month-olds, etc.) increased up to age 8 and 9 months, when the highest numbers of measles cases occurred (Figure 3). This was followed by a decrease in the number of cases among infants older than 9 months. This increasing incidence as infants get older is suggestive of declining maternal antibody levels with time. The decline in incidence that occurs after age 9 months correlated with MCV1 vaccination that begins to occur at age 9 months.

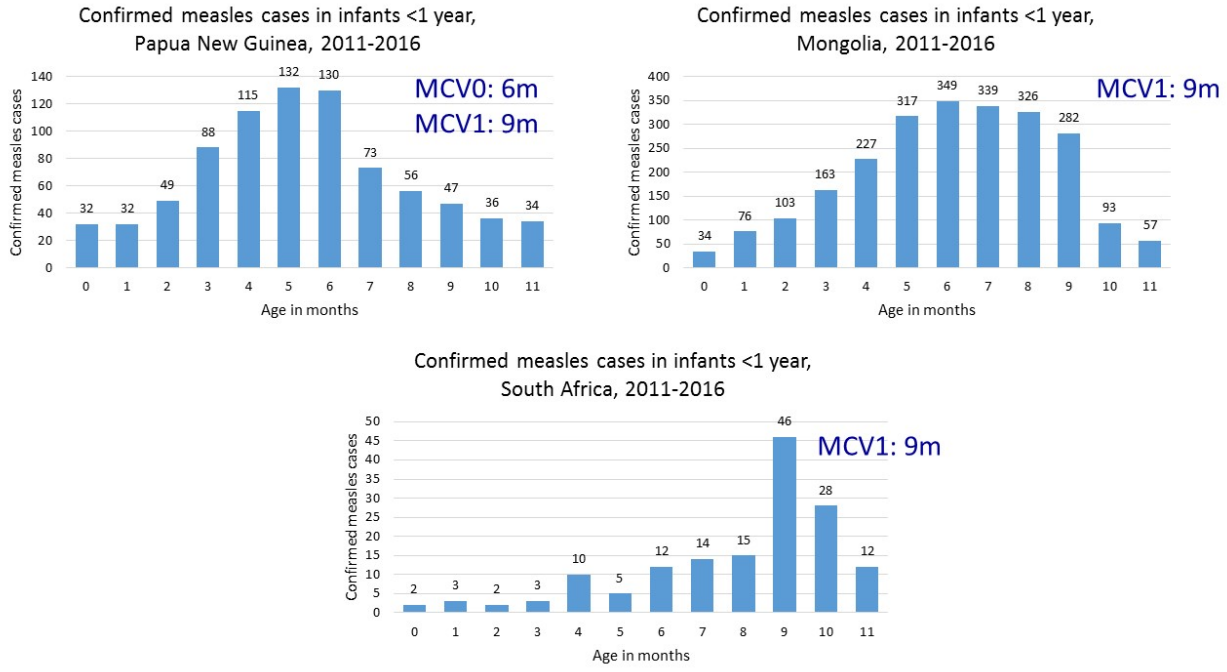


Figure 4. Ages of confirmed measles cases by month in Papua New Guinea, Mongolia, and South Africa, 2011-2016.

To illustrate this trend in three countries with high incidence of infant measles, we show measles cases by month for Papua New Guinea, Mongolia, and South Africa. In Papua New Guinea, where a zero dose of MCV is administered at age 6 months, the number of measles cases increased in each month up to age 6 months, then decreased after that (Figure 4). In South Africa, the number of measles cases increased in each month up to age 9 months, when MCV1 is administered, and then decreased. In Mongolia, the number of measles cases peaked at age 6 months, then plateaued until age 9 months, after which it decreased sharply.

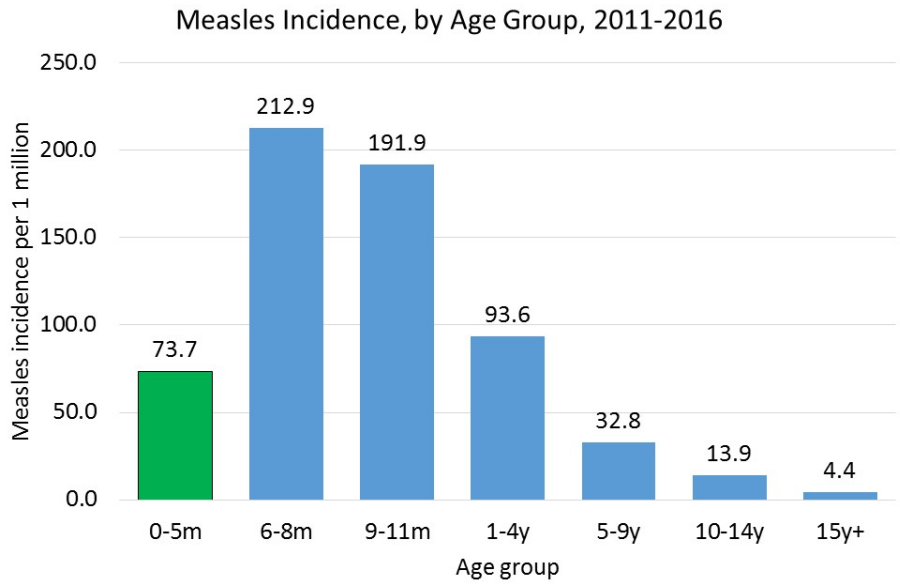


Figure 5. Age-specific average annual measles incidence per 1 million population, 2011-2016.

Average annual measles incidence among infants <6 months during 2011-2016 was 73.7 confirmed cases per 1 million population (Figure 5). Age-specific incidence was highest among 6-8-months-olds (212.9 per 1 million), followed by 9-11-month-olds (191.9 per 1 million). The age-specific incidence for infants <6 months was higher than that of older age groups including 5-9 years, 10-14 years, and ≥15 years.

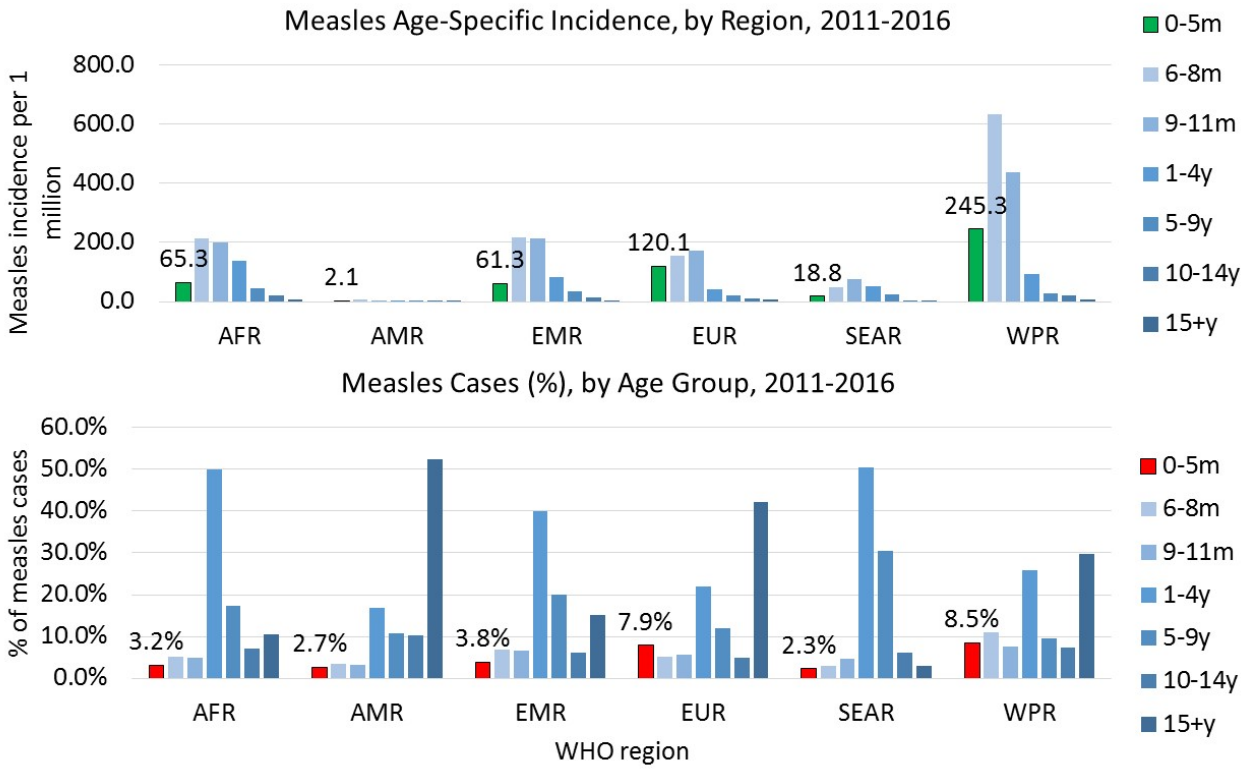


Figure 6. Age-specific incidence and percent of cases by age group, stratified by region, 2011-2016.

Compared to the overall <6-month incidence across all regions of 73.7 cases per 1 million, the two regions with highest <6-month incidences were EUR (120.1 per 1 million) and WPR (245.3 per 1 million) (Figure 6). The lowest <6-month incidence occurred in the Region of the Americas (AMR; 2.1 per 1 million).

Across all WHO regions, the highest age-specific incidence was among the 6-8 month age group and the 9-11 month age group (Figure 6), although in EUR there were just small differences in measles incidence between the <6-month, 6-8 month and 9-11 month age groups. In EUR and WPR regions, the incidence among infants <6 months was higher than the incidence among older children aged 1-4 years. In WPR, the region with the highest <6-month incidence (245.3 per 1 million), incidence in the <6 month age group was 2.5 times the incidence among the 1-4 year age group. The percentage of all measles cases that were <6 months was highest in EUR (7.9%) and WPR (8.5%), notably the same two regions with the highest incidences <6 months. The percentage of all measles cases that were <6 months ranged from 2.3% to 3.8% in the other regions.

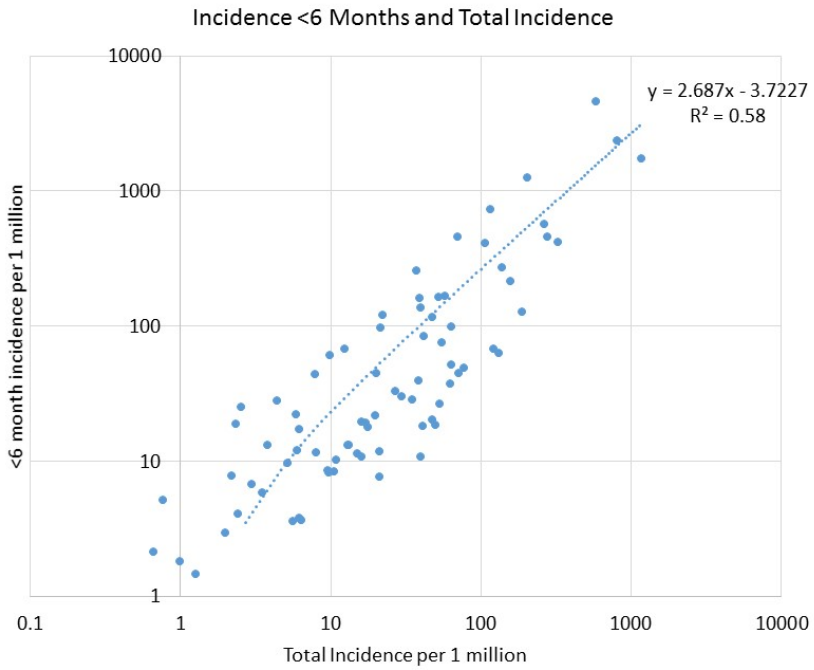


Figure 7. Correlation between incidence <6 months and total incidence (all ages), 2011-2016.

There was a strong and generally linear correlation between incidence in the <6 month age group and total incidence among all ages ($R^2 = 0.58$, $p<0.0001$) (Figure 7). In countries where overall incidence was high, <6-month incidence also tended to be high.

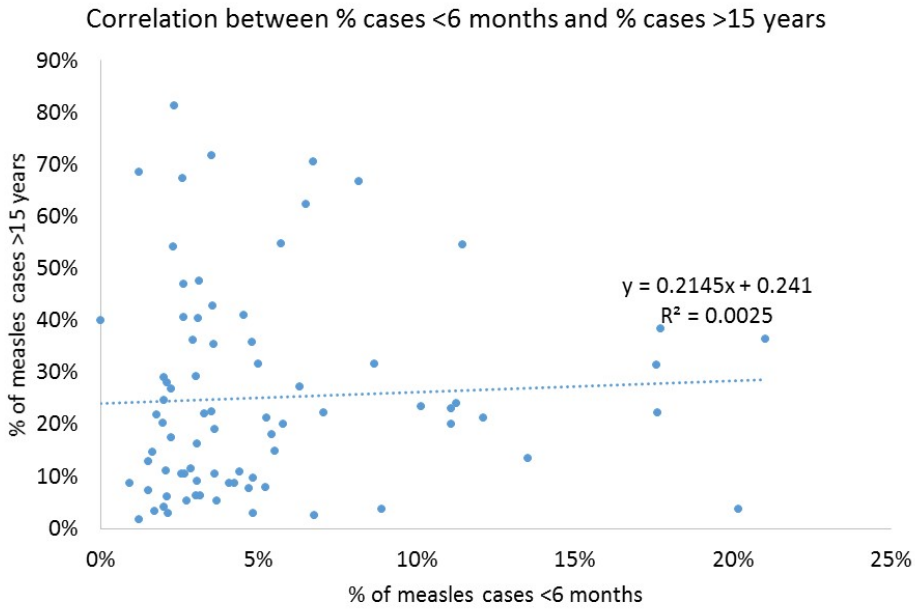


Figure 8. Correlation between the proportion of cases among infants <6 months and the proportion of cases >15 years, 2011-2016.

There was little correlation between the proportion of cases among infants <6 months and the proportion of cases >15 years in a country ($R^2 = 0.0025$) (Figure 8). When stratified by region, the EUR

region had the strongest correlation between the proportion of cases among infants <6 months and the proportion of cases >15 years in a country (R^2 = 0.1832), but correlations were not statistically significant in any region.

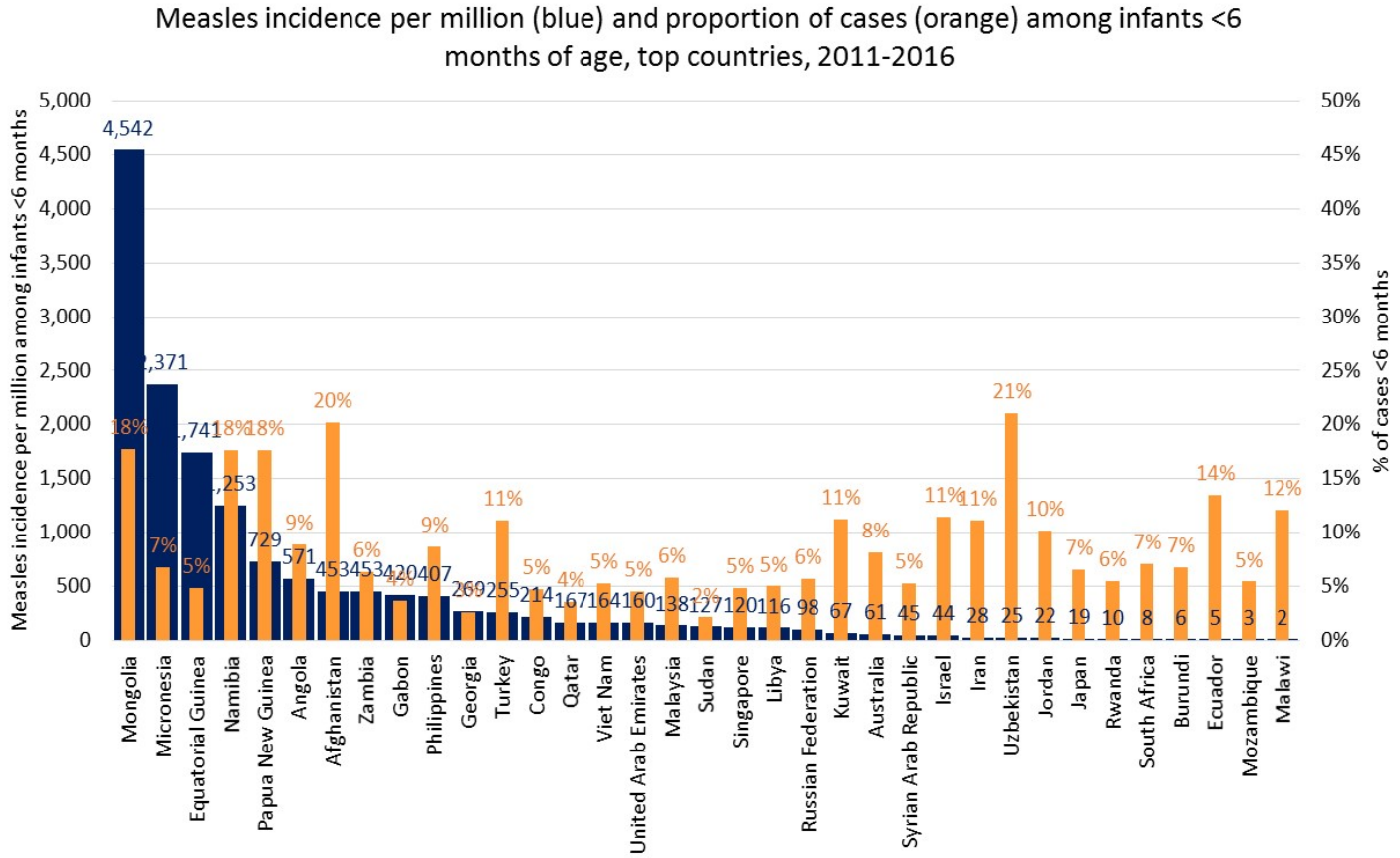


Figure 9. Measles incidence per 1 million and proportion of cases among infants <6 months of age, top countries, 2011-2016.

The countries with the highest <6-month average annual incidence during 2011-2016 were Mongolia, Micronesia, Equatorial Guinea, Namibia, and Papua New Guinea (Figure 9; shown in blue bars). All of these countries had large outbreaks at some point during 2011-2016 that dominated the country. The percentage of all confirmed cases that were <6 months ranged from 0% (Djibouti) to 21% (Uzbekistan). The average percent of cases among <6-month-olds in a country was 5.2%, and the median was 3.5% (Q1 - Q3: 2.3% - 6.1%).

Out of 80 countries included in the analysis, 26 countries had >5% of cases among infants <6 months. Twelve countries had >10% of cases <6 months. These included:

- EUR: Uzbekistan, Israel, Turkey
- EMR: Afghanistan, Kuwait, Iran, Jordan
- WPR: Mongolia, PNG
- AFR: Namibia, Malawi
- AMR: Ecuador

All countries with a high incidence of measles in infants <6 months did not necessarily have a high proportion of cases among infants <6 months. However, among the 10 countries with the highest <6-month incidences, in all but one >5% of cases were among <6-month-olds. In four of the highest-incidence countries, >10% of cases were among <6-month-olds.

Conversely, several countries had high proportions of cases among the <6 month age group, even though they did not have exceptionally high incidence rates in this age group. The two measures of measles in infants – <6-month incidence and proportion of cases among <6 months – measure different things, and may be important in different settings. Therefore, we decided to conduct regression analysis using both measures of measles in infants.

Bivariate (unadjusted) analysis of associations between country/programmatic characteristics and measles among infants <6 months

In bivariate regression, a few country and programmatic variables were statistically significantly associated with measles among infants <6 months (Figure 10).

Region. Countries in the WPR region had a significantly higher proportion of <6-month measles cases (ref: AFR), were 4.7 times more likely to have ≥5% of cases among the <6 month age group, and had higher age-specific incidence for <6-month-old infants.

Income. Upper middle income countries had a significantly higher proportion of <6-month measles cases (ref: low income), and was 6.3 times more likely for a country to have ≥5% of cases among the <6 month age group.

MCV1 coverage. Countries with a 5-year average MCV1 coverage ≥95% had a significantly higher proportion of <6-month measles cases (ref: <65%), and were 6.1 times more likely to have ≥5% of cases among the <6 month age group.

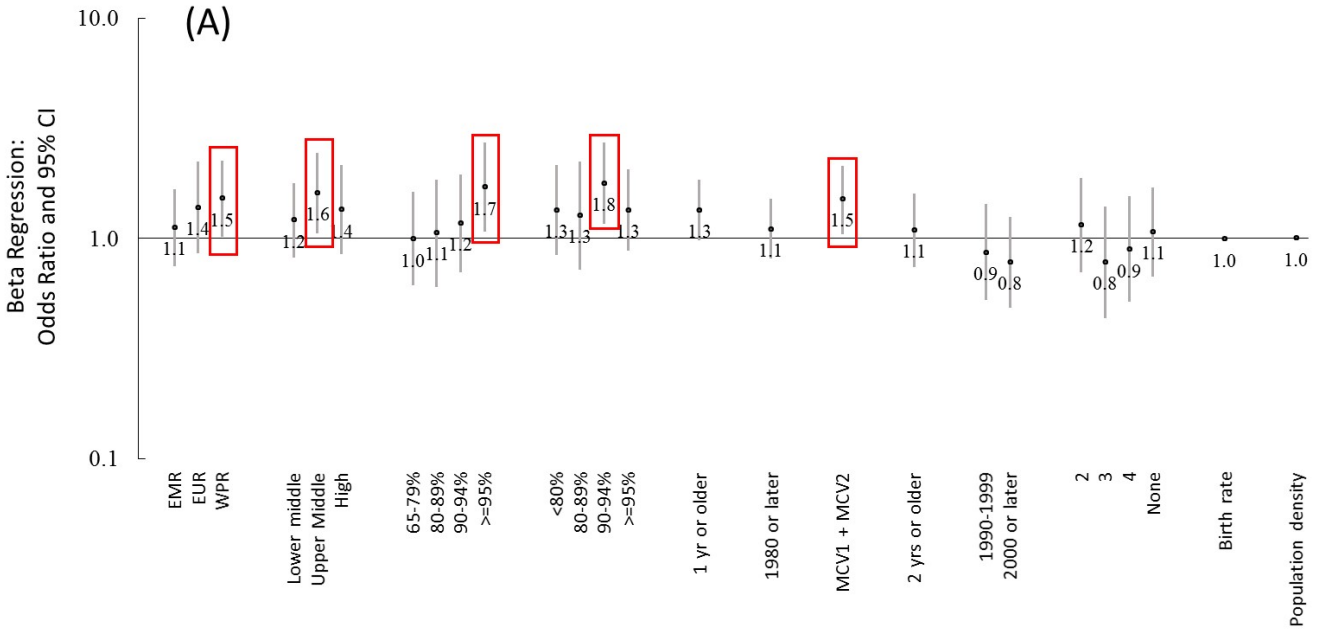
MCV2 coverage. Countries with a 5-year average MCV2 coverage 90-94% had a significantly higher proportion of <6-month measles cases (ref: MCV2 not administered). And countries with a 5-year average MCV2 coverage 80-89% or 90-94% were 8.5 and 6.4 times more likely, respectively, to have ≥5% of cases among the <6 month age group. Countries with a 5-year average MCV2 coverage 80-89% had higher age-specific incidence for <6-month-old infants, but other coverage categories were not significantly different with respect to age-specific incidence.

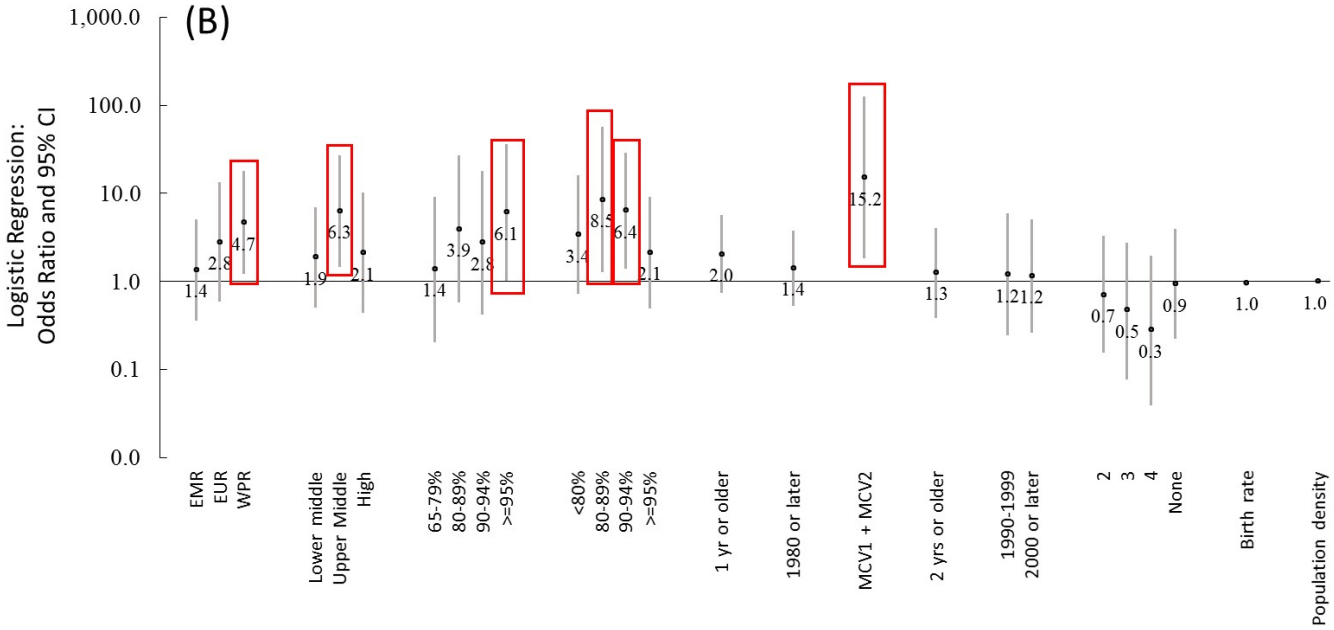
MCV2 status. Countries that have introduced MCV2 had a significantly higher proportion of <6-month measles cases (ref: have not introduced MCV2 yet), and were 15.2 times more likely to have ≥5% of cases among the <6 month age group.

Several of the country/programmatic characteristics that we analyzed had no statistically significant associations with any of the three measures of measles among infants <6 months of age:

- Age at MCV1 administration
- Year of MCV1 introduction
- Age at MCV2 administration
- Year of MCV2 introduction
- Years since last SIA

- Birth rate
- Population density





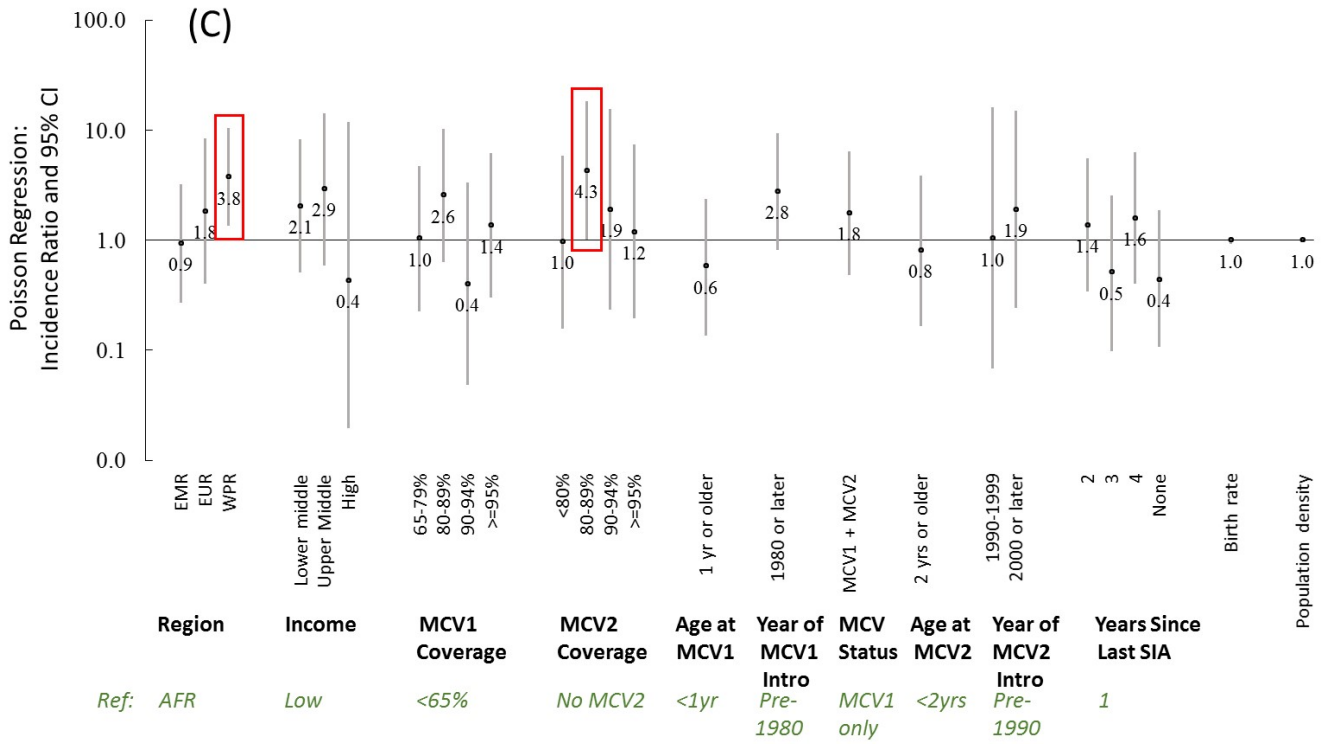


Figure 10. Results of bivariate (unadjusted) regression analysis using beta regression models to estimate odds ratios for proportion of cases <6 months (A), logistic regression models to estimate odds ratios for ≥5% (a "high" proportion) of cases <6 months (B), and poisson regression models to estimate incidence ratios for incidence among infants <6 months (C).
Note: Red boxes highlight statistically significant associations.

Multivariate (adjusted) analysis of associations between country/programmatic characteristics and measles among infants <6 months

In multivariate regression, variables were included in a fully adjusted model if they were significantly associated in at least one of the regression models. The covariates included in multivariate regression models were region, income, MCV1 coverage, MCV2 coverage, and MCV2 status. In multivariate models, many associations that were significant in bivariate models were attenuated (Figure 11). The only association that remained significant when adjusting for all other variables was MCV1 coverage. Countries with a 5-year average MCV1 coverage ≥95% had a significantly higher proportion of <6-month measles cases (ref: <65%), and were 18.5 times more likely to have ≥5% of cases among the <6 month age group.

	Beta regression: % of cases <6m	Logistic regression: ≥5% of cases <6m	Poisson regression: incidence per million <6m*
	OR (95% CI)	OR (95% CI)	IRR (95% CI)
Region (ref=AFR)			
EMR	0.71 (0.41-1.25)	0.18 (0.02-2.07)	1.25 (0.17-9.37)
EUR	0.87 (0.43-1.74)	0.12 (0.01-2.31)	1.54 (0.13-18.58)
WPR	1.12 (0.61-2.04)	1.51 (0.14-15.96)	5.37 (0.78-36.99)
World Bank income classification (ref=Low)			
Lower middle	1.12 (0.72-1.74)	0.98 (0.18-5.43)	1.43 (0.34-6.05)
Upper middle	1.29 (0.72-2.30)	7.19 (0.78-66.33)	4.27 (0.65-27.95)
High	1.13 (0.59-2.19)	0.54 (0.03-9.56)	1.19 (0.03-42.75)
MCV1 Coverage (ref=<65%)			
65-79%	0.88 (0.54-1.44)	0.43 (0.05-4.06)	0.92 (0.19-4.46)
80-89%	0.99 (0.57-1.73)	2.60 (0.31-21.63)	0.93 (0.16-5.51)
90-94%	1.24 (0.73-2.13)	2.83 (0.32-25.31)	0.26 (0.02-2.79)
≥95%	**2.04 (1.15-3.63)**	**18.50 (1.34-255.20)**	0.72 (0.03-16.01)
MCV2 Coverage (ref=no MCV2)			
<80%	1.68 (0.86-3.25)	12.17 (0.92-160.48)	0.53 (0.07-3.93)
80-89%	1.07 (0.46-2.46)	5.95 (0.26-138.65)	1.01 (0.11-9.15)
90-94%	1.07 (0.47-2.42)	3.43 (0.11-111.31)	0.44 (0.01-16.09)
≥95%	0.72 (0.34-1.54)	0.23 (0.01-4.29)	0.53 (0.02-13.57)

Figure 11. Results of multivariate (adjusted) regression analysis using beta regression models to estimate odds ratios for proportion of cases <6 months, logistic regression models to estimate odds ratios for ≥5% (a "high" proportion) of cases <6 months, and poisson regression models to estimate incidence ratios for incidence among infants <6 months.
Note: Red text highlights statistically significant associations.

Conclusions

During 2011-2016, there were almost 17,000 confirmed measles cases among infants <6 months in the countries included in our analysis. Since many countries were excluded due to missing age data, this is likely to be an underestimate of the total number of measles cases in infants <6 months. Infants <6 months comprise 4.3% of all confirmed measles cases, and have an age-specific average annual incidence of 73.7 per million. The majority of cases were in AFR and WPR countries (based on absolute numbers), and the highest age-specific incidence for infants <6 months was in WPR and EUR. Half of the countries studied had at least 3.6% of their cases among infants <6 months, and infants <6 months are disproportionately represented in measles cases compared to other age groups.

In bivariate unadjusted regression analyses, some characteristics were found to be associated with at least one of the measures indicating disproportionately more measles among infants <6 months compared to other ages. Specifically, countries with the following characteristics had either increased proportions of cases among infants <6 months or higher incidence among infants <6 months: WPR, upper-middle income, ≥95% MCV1 coverage, 80-89% or 90-94% MCV2 coverage, and MCV2 introduced.

In multivariate adjusted regression analyses, the only variable that was significant when adjusting for all other variables was ≥95% MCV1 coverage, which was associated with a higher proportion of cases among infants <6 months.

Limitations

This epidemiologic analysis of measles case-based surveillance data has several limitations. First, data from several countries were excluded from these analyses because they contained incomplete age data. This included a majority of EUR countries, and almost all SEAR countries. Consequently, some countries with recent large outbreaks (e.g., Romania) were not included in this analysis. It would be beneficial to be able to include such countries in the analysis. Second, the quality of some of the data used in this analysis may be sub-optimal. The sensitivity of the case-based surveillance data is unknown. Sensitivity of surveillance data may vary by age groups even within the same country, but we were not able to measure or estimate that. There may be reporting bias in which younger cases are more likely to be reported (younger infants may be more likely to have severe disease and require medical care). Vaccination coverage data estimates are based on countries' administrative data and WHO/UNICEF estimates, and the quality probably varies in different regions and/or countries. Third, surveillance data from India do not represent a truly case-based surveillance system, so those data were included in the epidemiologic analysis, but were not included in the regression analysis. Fourth, this was an ecologic analysis at the country level rather than an analysis of individual-level data. This limits our ability to investigate how individual level characteristics such as family composition or maternal immunization affect infants. Our results can only be generalized at the country level. Fifth, due to its observational nature, results from this study can imply only association, and not causation.

Future Research

Future research should attempt to determine the source of measles transmission to infants <6 months. Family structures and transmission patterns should be studied to determine whether these infant cases are primary or secondary cases in families, whether nosocomial transmission to infants is a problem, and the role of maternal immunity sourced from vaccination or infection. Answering these questions will help to determine whether infants <6 months must be protected directly through vaccination, or whether they can be protected indirectly by reducing or eliminating transmission in older children and adults. Outbreak investigations in which these data can be collected should be supported in representative communities.